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The evolution of image processing-powered hot-stage microscopy in pharmaceutical characterization

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Abstract

Hot-stage microscopy is essential for pharmaceutical characterization, revealing compounds' physical and chemical properties. It helps understand drug stability, purity, and formulation efficacy by observing melting points, polymorphic transformations, and crystallization events in real time in controlled heating samples. To analyze and interpret images, hot-stage microscopy relies on image processing. The process includes enhancement, filtering, segmentation, quantitative analysis, feature extraction, temperature mapping, real-time monitoring, image registration and alignment, and data visualization. As it evolves, hot-stage microscopy can improve drug development and patient outcomes. Hot-stage microscopy has revolutionized pharmaceutical characterization by directly observing the physical and chemical changes of drug substances during heating. This method illuminates melting points, phase transitions, polymorphism, and crystallinity, which affect drug stability, bioavailability, and efficacy. Future studies should explore more applications beyond crystalline phase analysis, amorphous phases, polymorphism, drug-excipient compatibility, and methodology optimization. Combining hot-stage microscopy with other analytical methods could lead to a more holistic approach to pharmaceutical characterization. The development of hot-stage microscopy presents promising opportunities for research and innovation in pharmaceutical science.

Keywords: Hot-stage microscopy, image processing, pharmaceutical, characterization, melting points, polymorphic

1. INTRODUCTION

Advancements in pharmaceutical characterization techniques, particularly the integration of hot-stage microscopy, have revolutionized the industry. As hot-stage microscopy has improved, it has become possible to look closely at pharmaceutical samples at high temperatures. This has given us important information about how they react to heat and change phases. This technique offers a unique perspective on the physical and chemical properties of pharmaceutical compounds, offering invaluable information for formulators and researchers. Hot-stage microscopy allows for real-time observation of melting points, polymorphic transformations, and crystallization events by subjecting samples to controlled heating. This real-time visualization offers a deeper understanding of drug stability, purity, and formulation efficacy. Furthermore, hot-stage microscopy has proven instrumental in the development of novel drug delivery systems and optimizing pharmaceutical formulations. Its continued advancement holds enormous promise for enhancing drug development processes and improving patient outcomes [1]–[8].

Pharmaceutical characterization uses hot-stage microscopy, a powerful analytical technique, to study the physical and chemical properties of materials as they undergo temperature changes. This method combines a microscope with a heating stage, enabling real-time observation of samples during heating or cooling. Researchers can gain valuable insights into the composition and behavior of the material under study by monitoring changes in the sample's appearance, such as melting, crystallization, or phase transitions. This technique is particularly useful in the pharmaceutical industry for investigating the thermal properties of drug substances, excipients, and formulations. Hot-stage microscopy can provide crucial information about the stability, purity, and compatibility of drug compounds, which is essential for ensuring the efficacy and safety of pharmaceutical products on the market [1], [5], [6], [8].

Furthermore, pharmaceutical characterization plays a crucial role in ensuring the quality, safety, and efficacy of drug products. We can thoroughly analyze the physical and chemical properties of pharmaceutical ingredients through techniques like hot-stage microscopy, which enhances our understanding of their behavior under various conditions. This knowledge is essential for the development of stable formulations, efficient manufacturing processes, and reliable drug delivery systems. Moreover, pharmaceutical characterization helps to identify potential impurities or degradation products that could impact the drug's performance or pose risks to patients. By investing in comprehensive characterization studies, pharmaceutical companies can ensure compliance with regulatory requirements, reduce development time, and ultimately bring high-quality medicines to market. In the complex and highly regulated field of drug development and manufacturing, pharmaceutical characterization plays a crucial role [1], [5], [6], [8].

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The evolution of hot-stage microscopy has been a key advancement in the field of pharmaceutical characterization. Originally developed in the mid-20th century, hot-stage microscopy allowed researchers to observe the melting and crystallization behavior of substances under controlled temperature conditions. Over time, improvements in technology have led to the development of more sophisticated hot-stage microscopy systems capable of precise temperature control and image analysis. These advancements have revolutionized the study of pharmaceutical materials, allowing for a more detailed understanding of their thermal properties and behavior. Hot-stage microscopy has become an indispensable tool in the pharmaceutical industry, enabling researchers to optimize drug formulations, study polymorphism, and investigate the stability of pharmaceutical compounds under various temperature conditions. As technology continues to advance, the future of hot-stage microscopy holds even more potential for furthering our understanding of pharmaceutical materials [9].

2. HISTORICAL DEVELOPMENT OF HOT-STAGE MICROSCOPY

The introduction of the first hot stages for optical microscopes in the early 20th century marked the historical development of hot-stage microscopy. To raise the temperature of the sample under observation, these early hot stages relied on simple heating elements. Over time, advancements in technology led to the integration of more precise temperature control systems and imaging capabilities, greatly enhancing the utility of hot-stage microscopy in pharmaceutical characterization. The ability to accurately observe and analyze material physical and chemical changes under controlled heating conditions has revolutionized pharmaceutical research and development. Today, hot-stage microscopes are essential tools for studying phase transitions, crystallization processes, and the thermal behavior of pharmaceutical compounds, providing valuable insights for drug formulation and quality control. We expect hot-stage microscopy to play an increasingly significant role in advancing pharmaceutical science and technology as it continues to evolve [10]–[14].

2.1. Early Beginnings of Hot-Stage Microscopy

In the early beginnings of hot-stage microscopy, researchers sought to overcome the limitations of traditional microscopy techniques by developing methods to observe physical and chemical changes in materials at elevated temperatures. One of the pioneering researchers in this field was Carl Zeiss, who introduced the first hot-stage microscope in the 1920s. This innovation allowed for the direct observation of phase transitions and melting points of various materials under controlled heating conditions. Subsequent advancements in optical microscopy and heating technology further improved the capabilities of hot-stage microscopy, making it an indispensable tool for studying the thermal behavior of pharmaceutical compounds. The integration of digital imaging and software analysis in recent years has further enhanced the precision and efficiency of hot-stage microscopy for pharmaceutical characterization. This evolution underscores the significant impact of early research and development efforts on the current state of hot-stage microscopy in pharmaceutical science [15], [16].

2.2. Milestones in the Advancement of Hot-Stage Microscopy

Throughout the history of hot-stage microscopy, significant milestones have marked the advancement of this analytical technique. One key development was the integration of video recording capabilities into hot-stage microscopes, allowing researchers to capture and analyze real-time images of sample transformations at elevated temperatures. This innovation greatly increased the efficiency and accuracy of data collection in hot-stage microscopy, enabling more precise characterization of pharmaceutical compounds and materials. Additionally, the introduction of sophisticated software for image analysis has revolutionized the interpretation of hot-stage microscopy results, providing quantitative data on phase transitions, melting points, and other critical parameters. These improvements have made hot-stage microscopy an important tool in pharmaceutical research and development. It gives us useful information about the thermodynamic properties and stability of drug formulations. As technology continues to evolve, hot-stage microscopy is poised to make even greater contributions to the field of pharmaceutical characterization [10]–[17]

2.3. Impact of Technological Innovations

Technological innovations have a significant impact on the evolving field of pharmaceutical characterization. Hot-stage microscopy, in particular, has seen significant advancements in recent years, thanks to the integration of cutting-edge technologies. Automation, advanced imaging techniques, and data analysis software have revolutionized the analysis of pharmaceutical samples. This has led to improved accuracy, efficiency, and reproducibility in the characterization process. Additionally, the ability to perform real-time observations and analysis has enabled researchers to gain valuable insights into the behavior of compounds under various conditions, ultimately contributing to a deeper understanding of their properties and performance. With these technological innovations, hot-stage microscopy has become an indispensable tool in

pharmaceutical research, allowing for enhanced product development and quality control processes. The ongoing growth and refinement of these technologies will undoubtedly continue to shape the future of pharmaceutical characterization [18].

2.4. Contributions to Pharmaceutical Research

In the realm of pharmaceutical research, various scientific disciplines have made significant contributions to advancing the field. Image processing plays a vital role in drug discovery and development, providing key insights into the characterization of the molecular structure of compounds and their interactions within biological systems. In parallel, materials science has facilitated the design of drug delivery systems with enhanced stability and efficacy. Moreover, engineering disciplines have driven innovation in pharmaceutical manufacturing, enabling the scale-up of production processes to meet growing demands. The collaboration between these diverse fields has fostered a holistic approach to pharmaceutical research, leading to the development of new drug formulations and therapies. By integrating expertise from chemistry, materials science, and engineering, especially image processing, researchers can address challenges in drug development more effectively, ultimately improving patient care and treatment outcomes. Such interdisciplinary collaboration is essential for overcoming the complex hurdles in pharmaceutical research and unlocking novel solutions for the ever-evolving healthcare landscape [15], [16], [19], [20].

3. HOT-STAGE MICROSCOPY IN PHARMACEUTICAL CHARACTERIZATION

Hot-stage microscopy has become an indispensable tool in pharmaceutical characterization due to its ability to provide valuable insights into the physical and chemical properties of drug substances. Hot-stage microscopy allows for real-time observation of phase transitions, melting points, polymorphic transformations, and crystallisation processes by subjecting samples to controlled temperature conditions. This information is crucial for assessing the stability, purity, and quality of pharmaceutical products, ultimately ensuring their efficacy and safety. Hot-stage microscopy can also help with formulation development by improving drug delivery systems and dealing with issues like how well drugs and excipients work together and how the particles are distributed in size. Overall, the applications of hot-stage microscopy in the pharmaceutical industry continue to expand, offering researchers a powerful tool for comprehensive drug analysis and optimization [1], [3]–[9].

3.1. Drug Polymorphism Studies

Hot-stage microscopy has made it much easier to study drug polymorphism by letting scientists look closely at crystal forms and phase changes in pharmaceutical materials. Drug polymorphism studies play a crucial role in assessing the physical and chemical properties of pharmaceutical compounds, impacting drug formulation, stability, and bioavailability. Researchers can observe the changes in crystal structure and morphology under varying temperature and humidity conditions using hot-stage microscopy, providing valuable insights into the behavior of different polymorphs. This level of analysis is essential for ensuring the quality and efficacy of pharmaceutical products, as different crystal forms can have distinct solubility and dissolution rates, affecting the drug's therapeutic effectiveness. Overall, the evolution of hot-stage microscopy has revolutionized the field of drug polymorphism studies, contributing to the development of safer and more effective medications [7].

3.2. Thermal Analysis of Pharmaceuticals

Thermal analysis of pharmaceuticals plays a crucial role in understanding the physical and chemical properties of drug compounds. By subjecting substances to varying temperatures, researchers can detect changes in the material's behavior, such as melting points, decomposition temperatures, and solid-state transitions. Hot-stage microscopy, a primary technique in thermal analysis, enables real-time observation of a sample during heating or cooling. This method provides valuable insights into the thermal behavior of pharmaceuticals, aiding in the identification of polymorphic forms, hydration states, and stability issues. Additionally, one can combine hot-stage microscopy with other analytical techniques like infrared spectroscopy or X-ray diffraction to gain a more comprehensive understanding of the sample under investigation. Overall, thermal analysis offers pharmaceutical scientists a powerful tool for characterizing drug substances and ensuring product quality and efficacy [15], [21]–[29].

3.3. Monitoring Phase Transitions

It is essential to closely monitor phase transitions during the pharmaceutical characterization process using hot-stage microscopy. By precisely controlling the temperature and observing the sample in real-time, researchers can identify any changes in crystal structure or melting points. This allows for a better

understanding of the thermal properties of the drug substance, which is crucial for determining its stability and efficacy. Furthermore, monitoring phase transitions is critical in assessing a drug's polymorphic forms, as different crystal structures can have varying pharmacokinetic properties. As noted, this detailed analysis can provide valuable insights into the behavior of a drug under different conditions, aiding in formulation development and quality control. In conclusion, the monitoring of phase transitions through hot-stage microscopy plays a critical role in pharmaceutical research and development [30]–[32].

3.4. Understanding Drug Formulation Processes

The complex process of drug formulation necessitates a multifaceted approach to addressing stability and efficiency concerns. Co-crystals, as discussed in [33], have emerged as an important tool in the pharmaceutical industry for improving the properties of active pharmaceutical ingredients. Researchers can create co-crystals with improved physicochemical properties by employing techniques such as Kofler fusion and co-grinding. This opens the door to new drug formulations. Unfortunately, the compounds are naturally weak, as evidenced by the lansoprazole pellets in [34]. This makes it difficult for drug delivery systems to remain stable. Researchers conduct meticulous investigations into formulation parameters and processing techniques in order to optimize the stability and efficacy of such dosage forms. When you combine advanced analytical tools and predictive models, such as the Arrhenius equation, you can gain a better understanding of how formulation factors affect drug stability and interact with one another. This information enables you to create more effective pharmaceutical products.

4. CHALLENGES AND FUTURE DIRECTIONS IN HOT-STAGE MICROSCOPY

In order to address the challenges and push forward the future directions of hot-stage microscopy in pharmaceutical characterization, it is essential to focus on advancements in technology, method development, and data analysis techniques. One of the main challenges is the need for improved resolution and sensitivity to accurately detect and characterize small drug particles or polymorphic forms during heating. To overcome this, researchers are exploring the use of higher-magnification lenses and advanced imaging software. Additionally, the development of automated hot-stage microscopy systems can streamline the process and allow for higher-throughput analysis, which is crucial for pharmaceutical research and development [9]. In the future, combining hot-stage microscopy with other analytical methods like Raman spectroscopy or X-ray diffraction could help us learn more about pharmaceutical materials when they are exposed to different temperatures. This could lead to more accurate drug formulation and production methods [2]–[5], [7], [8], [11], [12], [19], [21], [23], [26], [28], [29], [31], [32].

4.1. Limitations of Current Hot-Stage Microscopy Techniques

Another limitation of current hot-stage microscopy techniques is the inability to accurately mimic physiological conditions. These techniques observe drug behavior under controlled heating and cooling rates, but they fail to fully replicate the complex environment of the human body. This can lead to discrepancies between in vitro and in vivo results, making it challenging to predict actual drug behavior once administered to patients. Additionally, the resolution of hot-stage microscopy images can sometimes be limited, making it difficult to observe certain phenomena at the molecular level. To get around these problems, scientists are looking into new technologies that could make hot-stage microscopy better for characterizing pharmaceuticals. These include advanced imaging methods and the use of computer modeling. By overcoming these challenges, hot-stage microscopy has the potential to revolutionize the field of pharmaceutical research and development [2], [12], [15], [16], [25], [30].

4.2. Emerging Trends in Pharmaceutical Characterization

As hot-stage microscopy evolves, emerging trends in pharmaceutical characterization become more prominent within the industry. One of the key trends is the integration of advanced imaging techniques, such as confocal microscopy, to provide higher-resolution images and detailed information about the pharmaceutical samples under investigation. Additionally, there is a growing interest in utilizing artificial intelligence (AI) and machine learning algorithms to analyze the vast amounts of data generated by hot-stage microscopy, allowing for more accurate and efficient characterization of pharmaceutical materials. These innovations are paving the way for more automated and streamlined processes in pharmaceutical characterization, ultimately leading to faster drug development and improved product quality. As researchers continue to push the boundaries of hot-stage microscopy, these emerging trends demonstrate the potential for significant advancements in the field of pharmaceutical characterization [1], [3]–[9].

4.3. Integration of Hot-Stage Microscopy with Other Analytical Techniques

Furthermore, combining hot-stage microscopy with other analytical techniques has shown great promise in improving our understanding of pharmaceutical materials. Using hot-stage microscopy in conjunction with techniques such as Fourier-transform infrared spectroscopy (FTIR) and Raman spectroscopy, researchers can learn a lot about a sample's chemical make-up and structural properties all at once. This multidimensional approach enables a more in-depth analysis of pharmaceutical materials, resulting in a better understanding of their behavior under varying temperature conditions. For example, FTIR can provide information about specific functional groups in a sample, whereas hot-stage microscopy can reveal how these functional groups interact with temperature changes. By combining these techniques, researchers can gain a more comprehensive understanding of the material, ultimately improving the quality of pharmaceutical characterization [5], [6], [9], [24]

4.4. Potential for Advancements in Pharmaceutical Industry

With rapid technological advancements and an increasing understanding of molecular processes, the pharmaceutical industry has great potential for growth and innovation. Cutting-edge developments in areas such as personalized medicine, nanotechnology, and artificial intelligence are revolutionizing drug discovery, development, and delivery. For example, sophisticated drug delivery systems utilizing nanotechnology show promise in targeting drug delivery, enhancing efficacy, and minimizing side effects. Using AI in drug design and development also speeds up the process by predicting how drugs will interact with receptors and finding possible drug candidates more quickly and accurately than old ways of doing things. These advancements not only improve the efficiency of pharmaceutical research and development but also have the potential to significantly impact patient outcomes and healthcare systems on a global scale [9]. As technology continues to evolve, the possibilities for further advancements in the pharmaceutical industry are vast and exciting.

4.5. Hot stage microscopy (HSM) and Image Processing

Image processing plays a crucial role in supporting hot-stage microscopy (HSM) by enhancing the analysis and interpretation of the images obtained during the process. Here are several important roles that image processing plays in supporting HSM [15], [19], [20]:

1. Enhancement and Filtering: Image processing techniques can improve the quality of images captured during HSM. This includes noise reduction, contrast enhancement, and sharpening of features, which can make it easier to identify subtle changes in the sample's structure and behavior under varying temperatures.
2. Segmentation: Image segmentation techniques can separate different regions or phases within the sample based on their pixel intensity, color, or texture. This can aid in analyzing phase transformations or identifying specific areas of interest within the sample.
3. Quantitative Analysis: The data obtained from HSM. This includes measuring particle size, shape, and distribution, as well as tracking changes in these parameters over time or with temperature variations.
4. Algorithms for feature extraction can identify specific features of interest within the images, such as defects, boundaries between phases, or changes in morphology. This is particularly useful for studying phase transitions or material transformations.
5. Temperature Mapping: Researchers can correlate thermal profiles with structural changes seen under the microscope by using image processing to create temperature maps of the sample based on changes in pixel intensity or color.
6. Real-Time Monitoring: Some advanced setups use real-time image processing to dynamically monitor sample changes as temperature changes occur. This immediate feedback can aid in making decisions about the experiment or adjusting parameters in response to observed phenomena.
7. Image Registration and Alignment: Image processing techniques can align and register multiple images acquired over time or from different angles during HSM for accurate comparison and analysis.
8. Data Visualization: Image processing can generate visual representations of data, such as heat maps, histograms, or 3D reconstructions, which can provide insights into the sample's behavior and characteristics under varying thermal conditions.

Overall, image processing enhances the capabilities of hot-stage microscopy by enabling more detailed analysis, quantitative measurements, and visualization of the dynamic changes occurring in the sample at elevated temperatures. This helps researchers gain deeper insights into the thermal behavior and properties of the materials under study.

5. RESULTS AND DISCUSSION

The evolution of hot-stage microscopy has significantly impacted the field of pharmaceutical characterization. Initially developed in the early 20th century, hot-stage microscopy has undergone several key

advancements over the years. One of the major milestones was the incorporation of polarized light microscopy, allowing for better visualization of crystal structures and polymorphs. Subsequent improvements included the integration of heating and cooling capabilities, as well as automation for increased efficiency and accuracy. These developments have greatly enhanced the ability to study the thermal behavior and phase transitions of pharmaceutical compounds, leading to more precise insights into their stability and formulation. Hot-stage microscopy has become an indispensable tool in drug development, quality control, and formulation optimization. As technology continues to advance, the future of hot-stage microscopy holds promise for even more sophisticated applications in pharmaceutical research [1], [3]–[9].

Hot-stage microscopy has revolutionized the field of pharmaceutical characterization by allowing direct observation of the physical and chemical changes in drug substances during heating. This technique provides valuable insights into melting points, phase transitions, polymorphism, and crystallinity of pharmaceutical materials, which are crucial factors in determining drug stability, bioavailability, and efficacy. Through real-time visual data, researchers can analyze the behavior of drug compounds under varying temperature conditions, leading to a more comprehensive understanding of their properties. Additionally, hot-stage microscopy offers the advantage of being able to identify and distinguish between different pharmaceutical components in a mixture, aiding in formulation development and quality control processes. Overall, the significance of hot-stage microscopy in pharmaceutical characterization lies in its ability to provide detailed and precise information that is essential for ensuring the safety and efficacy of pharmaceutical products in the market [1], [7], [12], [27]

Moving forward, future research in the field of hot-stage microscopy in pharmaceutical characterization should focus on expanding the applications of this technique beyond just crystalline phase analysis [12]. By exploring the potential of hot-stage microscopy for the assessment of amorphous phases, polymorphism, and drug-excipient compatibility, researchers can provide a more comprehensive understanding of the physical and chemical properties of pharmaceutical formulations. Additionally, efforts should be made to optimize the methodology for hot-stage microscopy, including improving the resolution and sensitivity of the technique. Furthermore, investigations into the potential integration of hot-stage microscopy with other analytical methods, such as spectroscopic techniques and image processing, could lead to a more holistic approach to pharmaceutical characterization [1], [3]–[9]. These future research directions have the potential to significantly advance the field and enhance the quality of pharmaceutical development and manufacturing processes. Overall, the evolution and continued advancement of hot-stage microscopy offer promising opportunities for further exploration and innovation in pharmaceutical science.

6. CONCLUSION

Hot-stage microscopy (HSM) has significantly impacted pharmaceutical characterization, providing insights into the physical and chemical changes in drug substances during heating. This technique provides valuable insights into the melting points, phase transitions, polymorphism, and crystallinity of pharmaceutical materials, which are crucial factors in determining drug stability, bioavailability, and efficacy. Image processing plays a crucial role in supporting HSM by enhancing the analysis and interpretation of the images obtained during the process. Image processing techniques can improve the quality of images captured during HSM, including noise reduction, contrast enhancement, and sharpening of features. Image segmentation techniques can separate different regions or phases within the sample based on their pixel intensity, color, or texture, aiding in analyzing phase transformations or identifying specific areas of interest. Quantitative analysis of HSM data includes measuring particle size, shape, and distribution, as well as tracking changes in these parameters over time or with temperature variations. Feature extraction algorithms can identify specific features of interest within the images, such as defects, boundaries between phases, or changes in morphology. Temperature mapping allows researchers to correlate thermal profiles with structural changes seen under the microscope, creating temperature maps of the sample based on changes in pixel intensity or color. Real-time monitoring of sample changes as temperature changes occur is also possible through image registration and alignment. Future research in hot-stage microscopy for pharmaceutical characterization should focus on expanding the applications of this technique beyond just crystalline phase analysis. By exploring how hot-stage microscopy can test for amorphous phases, polymorphism, and drug-excipient compatibility, researchers can gain a deeper understanding of the chemical and physical properties of pharmaceutical formulations. Additionally, researchers should strive to enhance the hot-stage microscopy methodology by enhancing its resolution and sensitivity.

REFERENCES

[1] E. D. Freitas, J. M. M. Vidart, M. G. C. da Silva, and M. G. A. Vieira, "Thermal characterization and stability investigation of sericin and alginate blend loaded with diclofenac sodium or ibuprofen," *Eur. Polym. J.*, vol. 142, 2021, doi: 10.1016/j.eurpolymj.2020.110125.

[2] G. Zhu, J. Chen, J. Han, J. Li, Y. Li, and K. Liu, "Preparation, Characterization, and Desolvation of 5-Sulfoisophthalic Acid Sodium Salt Solvates," *Chem. Eng. Technol.*, vol. 45, no. 4, pp. 678–686, 2022, doi: 10.1002/ceat.202100576.

[3] A. Kumar and A. Nanda, "Similar but Not Same: Impact of Structurally Similar Coformers on Co-crystallization with Telmisartan," *J. Pharm. Innov.*, vol. 18, no. 4, pp. 1954–1965, 2023, doi: 10.1007/s12247-023-09759-w.

[4] B. A. Kondoros *et al.*, "Development of Solvent-Free Co-Ground Method to Produce Terbinafine Hydrochloride Cyclodextrin Binary Systems; Structural and In Vitro Characterizations," *Pharmaceutics*, vol. 14, no. 4, 2022, doi: 10.3390/pharmaceutics14040744.

[5] C. Zhao, W. Li, Z. Li, W. Hu, S. Zhang, and S. Wu, "Preparation and solid-state characterization of dapsone pharmaceutical cocrystals through the supramolecular synthon strategy," *CrystEngComm*, vol. 23, no. 38, pp. 6690–6702, 2021, doi: 10.1039/d1ce00945a.

[6] J. Deore, N. Rajput, T. Jadav, A. K. Sahu, and P. Sengupta, "Hot Stage Microscopy-based Method for Determination of Particle Size in Reverse Engineering: Establishment of a Platform Technology Employing Carvedilol as a Model Drug," *Curr. Anal. Chem.*, vol. 18, no. 10, pp. 1117–1130, 2022, doi: 10.2174/1573411018666220820095257.

[7] D. Salazar-Rojas, T. S. Kaufman, and R. M. Maggio, "A comprehensive approach toward concomitant triclabendazole polymorphism in pharmaceutical products," *J. Drug Deliv. Sci. Technol.*, vol. 62, 2021, doi: 10.1016/j.jddst.2021.102386.

[8] H. Liu, H. H. Y. Tong, and Z. Zhou, "Feasibility of thermal methods on screening, characterization and physicochemical evaluation of pharmaceutical cocrystals," *J. Therm. Anal. Calorim.*, vol. 147, no. 23, pp. 12947–12963, 2022, doi: 10.1007/s10973-022-11762-1.

[9] S. Qi, "Thermal Analysis of Pharmaceuticals BT - Analytical Techniques in the Pharmaceutical Sciences," A. Müllertz, Y. Perrie, and T. Rades, Eds. New York, NY: Springer New York, 2016, pp. 363–387. doi: 10.1007/978-1-4939-4029-5_11.

[10] S. C. Gad, C. B. Spainhour, and D. G. Serota, *Contract Research and Development Organizations-Their History, Selection, and Utilization*. Cham: Springer International Publishing, 2020. doi: 10.1007/978-3-030-43073-3.

[11] S. Singh *et al.*, "Elliptically birefringent chemically tuned liquid crystalline nanocellulose composites for photonic applications," *J. Mol. Liq.*, vol. 366, 2022, doi: 10.1016/j.molliq.2022.120326.

[12] H. Zhang, C. Qin, S. Nie, and S. Wang, "Effects of D-hot pretreatment on micro-distribution of residual lignin in sugarcane bagasse pulp and fiber properties," *Cellulose*, vol. 25, no. 8, pp. 4423–4435, 2018, doi: 10.1007/s10570-018-1883-3.

[13] M. C. Özdemir Yanık, O. Demirel, M. Elmadağlı, E. Günay, and S. Aydın, "Investigation of glass sintering to improve strength and interfacial interactions in glass-to-AISI 316L metal joints," *Int. J. Appl. Glas. Sci.*, vol. 14, no. 2, pp. 256–267, 2023, doi: 10.1111/ijag.16617.

[14] A. Afshanmehr, R. Najjar, E. Safari, and K. Asadpour-Zeynali, "Low driving-voltage four-armed pentaerythritol and coumarin based compounds as potential materials for LCDs," *Opt. Mater. (Amst).*, vol. 145, 2023, doi: 10.1016/j.optmat.2023.114439.

[15] G. P. Ashton, L. P. Harding, G. M. B. Parkes, and S. E. Pownall, "Application of hot-stage microscopy direct analysis in real time mass spectrometry (HDM) to the analysis of polymers," *Rapid Commun. Mass Spectrom.*, vol. 35, no. S2, 2021, doi: 10.1002/rcm.8522.

[16] I. A. C. Matias, "Automatic detection of characteristic viscosity points in mineralogical samples," in *Proceedings - 2016 International Conference on Computational Science and Computational Intelligence, CSCI 2016*, 2017, pp. 671–676. doi: 10.1109/CSCI.2016.0132.

[17] R. A. Carlton, *Pharmaceutical Microscopy*. Springer New York, 2011.

[18] R. A. Storey and I. Ymén, *Solid State Characterization of Pharmaceuticals*. Wiley, 2011.

[19] P. Pardhasaradhi, B. Taraka Phani Madhav, G. Srilekha, M. Ramakrishna Nanchara Rao, and G. Venkata Ganesh, "Identification of thermo optical parameters in 4l-hexyloxy-4-cyanobyphenyl with dispersed ZnO nano particles," *Zeitschrift fur Naturforsch. - Sect. A J. Phys. Sci.*, vol. 76, no. 10, pp. 947–957, 2021, doi: 10.1515/zna-2021-0046.

[20] J. Molnár *et al.*, "Structural investigation of semicrystalline polymers," *Polym. Test.*, vol. 95, 2021, doi: 10.1016/j.polymertesting.2021.107098.

[21] S. Burazer *et al.*, "Quenchable Porous High-Temperature Polymorph of Sodium Imidazolate, NaIm," *Cryst. Growth Des.*, vol. 21, no. 2, pp. 770–778, 2021, doi: 10.1021/acs.cgd.0c01006.

[22] F. Deslandes, A. Plana-Fattori, G. Almeida, G. Moulin, C. Doursat, and D. Flick, "Estimation of individual starch granule swelling under hydro-thermal treatment," *Food Struct.*, vol. 22, 2019, doi: 10.1016/j.foostr.2019.100125.

[23] S. Yeşilay, "Production of stoneware clay bodies by using industrial soda-lime-silica glass waste," *J. Aust. Ceram. Soc.*, vol. 55, no. 3, pp. 747–758, 2019, doi: 10.1007/s41779-018-0286-0.

[24] G. P. Ashton, L. P. Harding, and G. M. B. Parkes, "HDM, interfacing thermal analysis and ambient ionisation mass spectrometry," *J. Therm. Anal. Calorim.*, vol. 147, no. 18, pp. 10057–10065, 2022, doi: 10.1007/s10973-022-11322-7.

[25] G. Srilekha, P. Pardhasaradhi, B. T. P. Madhav, and M. R. Nanchara Rao, "Effect of ZnO nanoparticles on optical textures and image analysis properties of 7O.O5 liquid crystalline compound," *Zeitschrift fur Naturforsch. - Sect. A J. Phys. Sci.*, vol. 76, no. 4, pp. 349–359, 2021, doi: 10.1515/zna-2020-0302.

[26] J. Barberi *et al.*, "Robocasting of SiO2-based bioactive glass scaffolds with porosity gradient for bone regeneration

and potential load-bearing applications," *Materials (Basel).*, vol. 12, no. 7, 2019, doi: 10.3390/ma12172691.
[27] G. P. Ashton, L. P. Harding, G. Midgley, and G. M. B. Parkes, "Hot-stage microscopy - Direct Analysis in Real-time mass spectrometry (HDM) as a novel tool for monitoring thermally-driven reactions on a small scale," *Anal. Chim. Acta*, vol. 1128, pp. 129–139, 2020, doi: 10.1016/j.aca.2020.06.059.
[28] N. Moorthy and S. C. Murugavel, "Synthesis, characterization and photo – switching properties of azobenzene mesogen containing poly (ether - ester) s from cashew nut shell liquid," *J. Polym. Res.*, vol. 25, no. 3, 2018, doi: 10.1007/s10965-018-1449-y.
[29] A. C. Marsh, N. P. Mellott, M. Crimp, A. Wren, N. Hammer, and X. Chatzistavrou, "Ag-doped Bioactive Glass-Ceramic 3D Scaffolds: Microstructural, Antibacterial, and Biological Properties," *J. Eur. Ceram. Soc.*, vol. 41, no. 6, pp. 3717–3730, 2021, doi: 10.1016/j.jeurceramsoc.2021.01.011.
[30] P. Pardhasaradhi *et al.*, "Effect of ZnO nanoparticles on optical textures and image analysis properties of 7O.O5 liquid crystalline compound," *Zeitschrift fur Naturforsch. - Sect. A J. Phys. Sci.*, vol. 76, no. 4, pp. 349–359, 2021, doi: 10.1515/zna-2020-0302.
[31] R. Singh *et al.*, "Elucidating the Molecular Mechanism of Drug-Polymer Interplay in a Polymeric Supersaturated System of Rifaximin," *Mol. Pharm.*, vol. 18, no. 4, pp. 1604–1621, 2021, doi: 10.1021/acs.molpharmaceut.0c01022.
[32] J. Li, D. Bhattacharjee, X. Hu, D. Zhang, S. Sridhar, and Z. Li, "Crystallization Behavior of Liquid CaO-SiO2-FeO-MnO Slag in Relation to Its Reaction with Moisture," *Metall. Mater. Trans. B Process Metall. Mater. Process. Sci.*, vol. 50, no. 4, pp. 1931–1948, 2019, doi: 10.1007/s11663-019-01595-z.
[33] A. Alkhalil, "Application Of The Quality Control Methodologies To A Novel Solid Dosage Co-crystal Model System," The University Of Nottingham, 2013.
[34] M. Pašić, "Study to design stable lansoprazole pellets," University of Basel, 2008.